REACTION OF THE SODIUM SALTS OF SEVERAL HYDROXYPYRIMIDINES WITH α,ω-DIHALOALKANES

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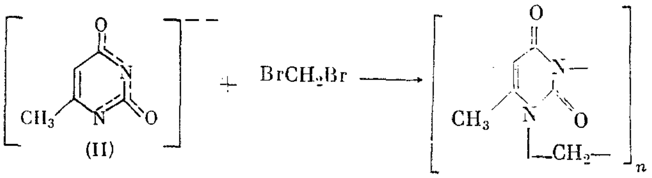
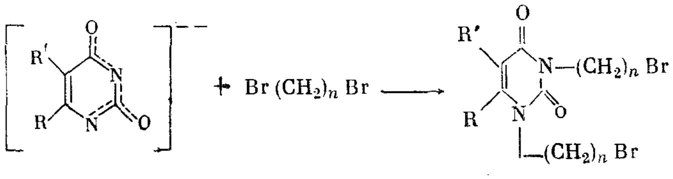
In order to synthesize N-(ω-haloaklyl)pyrimidines, which are the starting compounds for the synthesis of N-alkylpyrimidones with functional substituents in the alkyl chain, we investigated the reaction of the Na salts of uracil (I), 6-methyluracil (II), and several of their 5-substituted derivatives, as well as of 2-amino-4-hydroxy-6-methylpyrimidine (III) with a number of α,ω-dihaloalkanes. The reaction of the disodium salt of II with a tenfold excess of dibromomethane in absolute DMFA at 60-65°C results in the formation of a polymer (or mixture of oligomers), which does not contain the halogen, is infusible, and insoluble in water and organic solvents according to the scheme

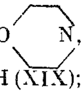


The formation of the polymer is apparently attributable to the strong electrophilic nature of the C atom in the CH_2 group in the initially formed N-bromomethyluracil, as a result of which the latter reacts with the next molecule of the sodium salt of II, despite the excess of CH_2Br_2. The reaction of the disodium salt of II with 1,2-dibromethane results in the formation of a resinous mass, from which it is not possible to isolate the N-(β-haloethyl)uracils.

The reaction of the sodium salts of uracils with 1,3-dibromopropane (IV), 1,4-dibromobutane (V), 1-bromo-4-chlorobutane (VI), 1,5-dibromopentane, and 1,6-dibromohexane yields N-(ω-haloalkyl)uracils only with specific proportions between the starting components and only at a definite temperature. For example, the reaction of the disodium salts of uracils with an eight- to tenfold molar excess of the α,ω-dihaloalkane in absolute DMFA at 25-80°C produces 1,3-bis(ω-haloalkyl)uracils (46-60% yields):



(VII)—(XX)

$n = 3$, $R'=R=H$ (VII); $n = 3$, $R'=H$, $R=CH_3$ (VIII); $n = 4$, $R'=R=H$ (IX); $n = 4$, $R'=CH_3$, $R=H$ (X); $n = 4$, $R'=H$, $R=CH_3$ (XI); $n = 4$, $R'=H$, $R=CH_3$ (XII);* $n = 5$, $R'=H$, $R=CH_3$ (XIII); $n = 6$, $R'=H$, $R=CH_3$ (XIV); $n = 4$, $R'=NO_2$, $R=CH_3$ (XV); $n = 4$, $R'=C_6H_5NH$, $R=H$ (XVI); $n = 4$, $R'=$  O N, $R=H$ (XVII); $n = 4$, $R'=CH_3C(O)$, $R=H$ (XVIII); $n = 4$, $R'=CH_3OC_6H_4NH$, $R=H$ (XIX); $n = 4$, $R'=C_6H_5NH$, $R=CH_3$ (XX)

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* $Hal^1 = Br$, $Hal^2 = Cl$.

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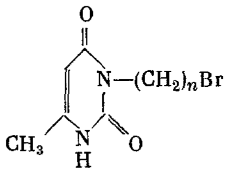
Compounds VII through XX are crystalline compounds or transparent oils, which are highly soluble in ether, benzene, and $CHCl_3$. In accordance with their structures, the IR spectra of compounds VII through XX display two intense bands at $\nu_{C=O}$ (1650-1680 and 1700-1710 cm^{-1}), and there are no vibrations at all in the 3100-3600 cm^{-1} region (ν_{NH} and ν_{O-H}).

The reaction of the disodium salt of II with IV and V along with 1,3-bis(ω-haloalkyl)-uracils produced 3-(3-bromopropyl)-6-methyluracil (XXI) and 3-(4-bromobutyl)-6-methyluracil (XXII), respectively (6-12% yields)

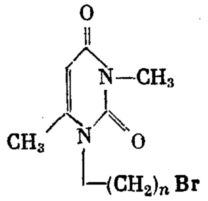


$n = 3$ (XXI), 4 (XXII)

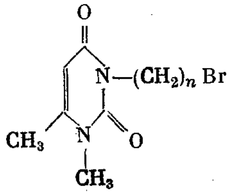
Compounds XXI and XXII are crystalline substances, which are soluble in benzene to a limit and soluble in $CHCl_3$ and alcohols. The IR spectra of XXI and XXII have two intense absorption bands at $\nu_{C=O}$ (1640-1660 and 1700-1715 cm^{-1}) and a ν_{N-H} band with a maximum at 3080-3100 cm^{-1}. The absorption maximum in the UV spectra of XXI and XXII show a bathochromic shift of 22 to 23 nm, as the ambient pH is varied from 2 to 12 ($\lambda_{max} = 261$-263 nm at pH 2 and $\lambda_{max} = 284$-285 nm at pH 12). This is characteristic of uracils with substitutients on the third ring nitrogen atom [1].

A decrease in the amount of the dihaloalkane introduced into the reaction or an increase in the reaction temperature to above 80°C results in a sharp drop in the yields of the 1,3-bis(ω-haloalkyl) uracils. For example, in the case of the reaction of the disodium salts of I and II with a two- to threefold excess of IV, the yields of VII and VIII are 15-18%.

The sodium salts of 1(3),6-dimethyluracils react with four- to fivefold excesses of α,ω-dibromoalkanes at 25-60°C to form the respective N-(ω-bromoalkyl)uracils (XXIII through XXVI) with 65-75% yields

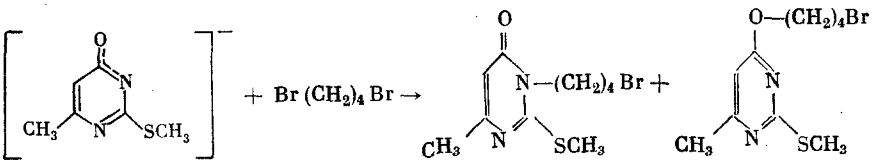


$n = 3$ (XXIII), 4 (XXIV)



$n = 3$ (XXV), 4 (XXVI)

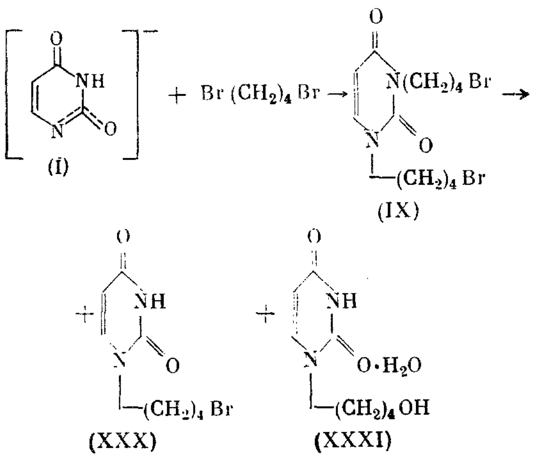
Unlike the N-methyluracils, the sodium salt of 2-methylthio-4-hydroxy-6-methylpyrimidine (XXVII) reacts with an excess of V in absolute DMFA at 25-50°C to form a mixture of 2-methylthio-3-(4-bromobutyl)-4-oxo-6-methyl-3,4-dihydropyrimidine (XXVIII) and 2-methylthio-4-(4-bromobutyl)oxy-6-methylpyrimidine (XXIX) (the yields are 19 and 53%, respectively) according to the scheme



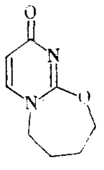
(XXVII) (XXVIII) (XXIX)

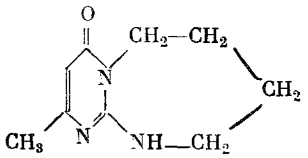
The IR spectrum of XXVIII shows a $\nu_{C=O}$ band at 1680 cm^{-1}, and there are no vibrations in this region in the spectrum of XXIX.

The reaction of the monosodium salts of the uracils with α,ω-dihaloalkanes proceeds with the predominant formation of 1,3-bis(ω-haloalkyl)uracils; however, the yields of the latter are poorer than in the case of the disodium salts of the uracils. For example, the reaction of the monosodium salt of II with a fourfold molar excess of V in absolute DMFA at 30-60°C results in the formation of a mixture of compounds XI (35% yield) and (XXII) (6% yield). The reaction of the monosodium salt of I with a three- to fourfold molar excess of V under similar conditions results in the formation of 1,3-bis(4-bromobutyl)uracil (IX), 1-(4-bromobutyl)uracil (XXX), and 1-(4-hydroxybutyl)uracil (XXXI) (in the form of the monohydrate) with 19, 17, and 7% yields, respectively, according to the scheme



The compounds obtained were separated by chromatography in a column with Al_2O_3. The IR spectrum of XXXI shows a ν_{OH} band of the alcohol group (3200 cm^{-1}) and a ν_{OH} band of the water of hydration (3500 cm^{-1}). The absorption maxima in the UV spectra of XXX and XXXI do not show a bathochromic shift as the ambient pH is varied from 2 to 12 ($\lambda_{max} = 266$-269 nm), indicating that the substitution occurs at the first nitrogen atom in the pyrimidine ring [1-3]. The formation of XXXI is apparently associated with the intramolecular cyclization of XXX to form 2-oxopyrimido[1,2-b]perhydro-9,10-oxazepine (XXXII), whose unstable seven-member ring opens under the action of water during the treatment of the reaction mass


(XXXII)


(XXXIII)

The reaction of the sodium salt of III with an excess of 1,4-dibromobutane results in the formation of a complex mixture, from which it has been possible to isolate only 9-methyl-7-oxopyrimido[2,3-a]perhydro-1,6-diazepine (XXXIII) (9% yield). Compound XXXIII is soluble in ether, benzene, and $CHCl_3$, and its IR spectrum shows a $\nu_{C=O}$ band (1670 cm^{-1}) and a ν_{NH} band (3240 cm^{-1}).

EXPERIMENTAL

The IR spectra were recorded on a UR-10 spectrophotometer. The solids were examined in the form of suspensions in liquid petrolatum, and the liquids were examined in the form of films between KBr plates. The UV spectra were recorded on a Specord UV-VIS spectrophotometer. Neutral Al_2O_3 (second activity classification) was used for the column chromatography. The properties of the compounds synthesized are given in Table 1.

General Method for Reacting the Sodium Salts of the Uracils with the α,ω-Dihaloalkanes. One mole (0.5 moles in the case of the disodium salts) of the respective uracil was added to a solution of 1 mole of Na in 1.5 to 2.0 liters of absolute propanol or n-butanol, and the mixture was boiled for 4-5 h until the mass was homogenized. The solvent was driven off in a vacuum, and the residue was removed azeotropically with benzene. Then 1 liter of absolute DMFA was added to the dry sodium salt, the mixture was stirred for 0.5 h, and 4-5 moles (8-10 moles in the case of the disodium salts) of the α,ω-dihaloalkane were added. The mass was stirred for 7-8 h at 45-65°C to a pH of 7. The solution was filtered from the precipitate, the filtrate was evaporated in a vacuum, and the residue was treated with benzene or $CHCl_3$. The filtrate was evaporated down to 30-50 ml and chromatographed in a column with Al_2O_3.

TABLE 1

Compound	Yield, % of the theoret.	mp, °C or n_D^{20}	$\frac{\text{Found}}{\text{Calculated}}$, % C	H	N	Hal	Empirical formula
(VII)	18	1,5657	$\frac{33,57}{33,90}$	$\frac{3,72}{4,00}$	$\frac{8,03}{7,90}$	–	$C_{10}H_{14}Br_2N_2O_2$
(VIII)	15	1,5720	–	–	$\frac{8,17}{7,60}$	$\frac{43.45}{43,50}$	$C_{11}H_{16}Br_2N_2O_2$
(IX)	59	1,5600	$\frac{37,96}{37,70}$	$\frac{4.76}{4,71}$	$\frac{7.26}{7,33}$	$\frac{41,71}{41,89}$	$C_{12}H_{18}Br_2N_2O_2$
(X)	54	1,5542	$\frac{39,42}{39,39}$	$\frac{5,02}{5,05}$	$\frac{7.12}{7,05}$	$\frac{40,42}{40,40}$	$C_{13}H_{20}Br_2N_2O_2$
(XI)	48	64–66	–	–	$\frac{7,57}{7,05}$	$\frac{40,46}{40,40}$	$C_{13}H_{20}Br_2N_2O_2$
(XII)	54	61–62	$\frac{44,19}{44,35}$	$\frac{5.58}{5,68}$	$\frac{8,18}{7,96}$	$\frac{33.25^{*}}{32.94}$	$C_{13}H_{20}BrClN_2O_2$
(XIII)	55	1,5512	$\frac{42.48}{42,45}$	$\frac{5,88}{5,65}$	$\frac{6,68}{6,60}$	$\frac{37.68}{37,70}$	$C_{15}H_{24}Br_2N_2O_2$
(XIV)	50	1,5380	–	–	$\frac{6,29}{6,18}$	$\frac{35,71}{35,32}$	$C_{17}H_{28}Br_2N_2O_2$
(XV)	46	61–62	$\frac{35.62}{35,41}$	$\frac{4,53}{4,32}$	$\frac{9,85}{9,85}$	–	$C_{13}H_{19}Br_2N_3O_4$
(XVI)	45	1.6120	$\frac{45,80}{45,71}$	$\frac{5,12}{5,30}$	$\frac{8,51}{8,90}$	–	$C_{18}H_{23}Br_2N_3O_2$
(XVII)	46	Viscous oil	$\frac{41,95}{42,50}$	$\frac{5,37}{5,10}$	$\frac{9,02}{8,74}$	–	$C_{17}H_{27}Br_2N_3O_3$
(XVIII)	52	1,5670	$\frac{39,47}{39,00}$	$\frac{5,26}{5,21}$	$\frac{6,73}{6,58}$	$\frac{37,25}{37,70}$	$C_{14}H_{20}Br_2N_2O_3$
(XIX)	50	1.6078	$\frac{45.64}{45,34}$	$\frac{5,32}{5,00}$	$\frac{8,56}{8,35}$	–	$C_{19}H_{25}Br_2N_3O_3$
(XX)	51	1,5920	$\frac{47,20}{46,80}$	$\frac{5,47}{5,10}$	$\frac{8,55}{8,60}$	–	$C_{19}H_{25}Br_2N_3O_2$
(XXI)	12	204–206	–	–	$\frac{11,55}{11,30}$	$\frac{31,93}{32,40}$	$C_8H_{11}BrN_2O_2$
(XXII)	6,0	174–175	$\frac{41.26}{41,40}$	$\frac{5,02}{4,98}$	$\frac{10,59}{10,73}$	$\frac{30,73}{30,61}$	$C_9H_{13}BrN_2O_2$
(XXIII)	71	102–103,5	$\frac{41,56}{41,40}$	$\frac{5,17}{5,00}$	$\frac{11,09}{10,70}$	–	$C_9H_{13}BrN_2O_2$
(XXIV)	66	70,5–72	–	–	$\frac{10,42}{10,18}$	$\frac{28,89}{29,08}$	$C_{10}H_{15}BrN_2O_2$
(XXV)	77	73–74	$\frac{41,49}{41,50}$	$\frac{5,05}{5,00}$	$\frac{10,74}{10,70}$	–	$C_9H_{13}BrN_2O_2$
(XXVI)	75	88–90	–	–	$\frac{10,16}{10,18}$	$\frac{28,68}{29,08}$	$C_{10}H_{15}BrN_2O_2$
(XXVIII)	19	1,5746	$\frac{41,35}{41,20}$	$\frac{5,21}{5,15}$	$\frac{9,63}{9,61}$	$\frac{10,89^{\dagger}}{10,98}$	$C_{10}H_{15}BrN_2SO$
(XXIX)	53	1,5600	$\frac{41,34}{41,20}$	$\frac{5,26}{5,15}$	$\frac{9,88}{9,61}$	$\frac{11,04^{\dagger}}{10,98}$	$C_{10}H_{15}BrN_2SO$
(XXX)	17	93–94	$\frac{39,20}{38,80}$	$\frac{4,58}{4,45}$	$\frac{11,53}{11,40}$	–	$C_8H_{11}BrN_2O_2$
(XXXI)	7	1,5642	$\frac{47,82}{47,50}$	$\frac{6.43}{6,40}$	$\frac{13,28}{13,80}$	–	$C_8H_{14}N_2O_4$
(XXXIII)	9	128–129	$\frac{60.41}{60,00}$	$\frac{7,12}{7,20}$	$\frac{23.26}{23,50}$	–	$C_9H_{13}N_3O$

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*The Cl + Br content is indicated.

†The S content is indicated.

The column was washed successively with petroleum ether, ether, benzene, $CHCl_3$, and propanol. The corresponding 1,3-bis(ω-haloalkyl)uracil was obtained following the evaporation of the ethereal fractions. The 3(1)-(ω-haloalkyl)uracil was obtained following the evaporation of the $CHCl_3$ fractions.

The reaction of the 1(3),6-dimethyluracils and 2-methylthio-4-hydroxy-6-methylpyrimidine with α,ω-dibromoalkanes and the isolation of the reaction products were carried out in an analogous manner. The products XXI, XXII, and XXX were eluted from the column by $CHCl_3$ and recrystallized from benzene or xylene; XXXI was eluted by propanol, and XXIII and XXIV were eluted by benzene and recrystallized from a petroleum ether—benzene mixture. Compound XXIX was eluted by petroleum ether, and XXVIII was eluted by ether. Products XXV and XXVI were purified by recrystallization from a petroleum ether—benzene mixture without preliminary chromatography.

Reaction of the Na Salt of III with V. A 20 g portion of III was added to a solution of 3.7 g of Na in 200 ml of absolute n-butanol, and the mixture was boiled for 2 h until the mass was homogenized. Then 80 ml of V were added, and the mixture was boiled with stirring for 1.5 h to a pH of 7. The precipitate formed was filtered, the filtrate was evaporated in a vacuum, and the residue was treated with $CHCl_3$ and filtered. The filtrate was evaporated down to 30 ml and chromatographed on Al_2O_3. The column was washed successively with petroleum ether, ether, benzene, and $CHCl_3$. Evaporation of the ether fractions (two 500-ml portions) yields 2.6 g (9.0%) of XXXIII, mp 128-129°C (from a petroleum ether—benzene mixture).

CONCLUSIONS

A simple one-step method for the synthesis of 1,3-bis(ω-haloalkyl)uracils by reacting the Na salts of uracil and its derivatives with α,ω-dihaloalkanes has been developed.

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SYNTHESIS AND PROPERTIES OF PYRIMIDINYLALKYLSULFONAMIDES.

2. REACTION OF SEVERAL HYDROXYPYRIMIDINES WITH N-PHENYL-N-METHYL-ω-CHLOROALKYLSULFONAMIDES

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As a continuation of our investigations on the synthesis of pyrimidinylalkylsulfonamides, we studied the reaction of several hydroxypyrimidines with N-phenyl-N-methyl-4-chlorobutylsulfonamide (I) and with N-phenyl-N-methyl-3-chloropropylsulfonamide (II). The reaction of the dry sodium salts of uracil (III) and 6-methyluracil (IV) with I and II in boiling abs. DMFA yields the corresponding N-[ω-(N'-phenyl-N'-methylsulfonamido)alkyl]uracils (V through XII) as the main products (see scheme on next page).

In accordance with their structure, the IR spectra of V through XII show two intense bands in the $\nu_{C=O}$ region (1660-1670 and 1700-1720 cm^{-1}) in analogy to the N-alkyluracils [1]; ν_s and ν_{as} of the SO_2 groups appear at 1149-1151 and 1330-1352 cm^{-1}, respectively [2];

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